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ORTHO-McNEIL

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DOCKET NO. 2005P-0352: SUPPLEMENT TO CITIZEN PETITION

On August 29, 2005, Ortho Urology, a unit of Ortho-McNeil Pharmaceutical, Inc, submitted a Citizen Petition (Petition) under section 505 of the Federal Food, Drug, and Cosmetic Act, and 21 CFR § 10.30. The Petition requested that the Commissioner of the Food and Drug Administration (FDA) require that standard bioequivalence criteria be applied separately to oxybutynin and its active metabolite, desethyloxybutynin, to ensure that approved generic versions of DITROPAN XL® (oxybutynin chloride) Extended-Release tablets are both bioequivalent and clinically equivalent to the innovator product.

Collective scientific and clinical evidence from *in vitro*, animal, and well-controlled clinical studies submitted in the Petition demonstrates that oxybutynin's major metabolite, desethyloxybutynin, is formed by presystemic gut-wall metabolism and that this metabolite contributes meaningfully to the safety and efficacy profiles. Reliance upon average bioequivalence of oxybutynin alone may result in inappropriate bioequivalence determinations for this type of extended-release product, suggestive of a potential bioequivalence problem that warrants assessment under 21 CFR § 320.33 (f).

In this Petition Supplement, submitted under 21 CFR § 10.30(g), Ortho Urology provides evidence from additional analyses of biopharmaceutical study data that supports the original request for FDA to require bioequivalence criteria be applied to both oxybutynin and desethyloxybutynin. In these same analyses, other results signal the potential for differences among extended-release oxybutynin products in that the R- and/or S-enantiomer exhibits nonlinear absorption due to drug input rate. Oxybutynin, therefore, meets the four conditions upon which FDA recommend[1] that bioequivalence of individual enantiomers be determined.

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[1] FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. March 2003. pp 18-19.

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- A recently completed statistical analysis of metabolite-to-parent ratios for racemic drug and each enantiomer show that they are significantly higher for immediate-release tablets than those for DITROPAN XL. These findings further support Ortho Urology's original request to apply bioequivalence criteria to both oxybutynin and desethyloxybutynin, especially to extended-release products that release drug at different *in vitro* and/or *in vivo* rates and locations along the gastrointestinal tract.

- Additionally, the statistical analyses compared enantiomer (R-to-S) concentration ratios for oxybutynin and desethyloxybutinin between immediate-release and DITROPAN XL tablets, which demonstrate that the enantiomer concentration ratio changed with the drug's input rate. Ortho Urology, therefore, requests that FDA require, rather than recommend[2], that bioequivalence criteria be applied separately to the R- and S-enantiomers of both oxybutynin and desethyloxybutynin to ensure bioequivalence and true therapeutic equivalence of extended-release oxybutynin products. Moreover, application to the four active moieties[3] of oxybutynin should be required in bioequivalence studies conducted under both fasting and fed conditions.

At the time of this Supplement, a generic pharmaceutical firm provided comments[4] on Ortho Urology's original Petition. They concur that oxybutynin's major metabolite, desethyloxybutinin, is formed as a result of gut-wall pre-systemic metabolism, and that it contributes meaningfully to safety and efficacy. However, they believe that metabolite data should remain supportive, and cite FDA's guidance statement[5] that parent drug is more sensitive to formulation changes. We believe that the latter is not true for certain chiral drugs, including oxybutynin, in which there is nonlinear absorption of either or both enantiomers such that R-to-S concentration ratios of the parent and metabolite change with drug input rate. The drug input rate is a function of the delivery system, release rate, rate of gut wall metabolism and absorption, and gastrointestinal transit time (which is especially important for site-specific gut wall metabolism).

Moreover, Ortho Urology agrees with the statements by the generic pharmaceutical firm that bioequivalence of the oxybutynin enantiomers should be determined when all four conditions cited in FDA's guidance[6] is met. Scientific and clinical evidence, provided in the

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[2] Ibid 1

[3] 21 CFR § 320.24(b)(1)(i).

[4] Comments to Docket No. 2005T-0352 by Mylan Pharmaceuticals Inc. October 3, 2005

[5] Ibid 1.

[6] Ibid 1.

original Petition and summarized herein, shows that the oxybutynin enantiomers exhibit different pharmacokinetic and pharmacodynamic characteristics, and that the primary safety and efficacy activity resides with the minor enantiomer (R-oxybutynin). In this Supplement, Ortho Urology presents scientific evidence demonstrating that oxybutynin exhibits nonlinear absorption in which the enantiomer concentration ratio changes with the drug input rate. Oxybutynin is a chiral drug that meets the four conditions for which bioequivalence of individual enantiomers should be determined.

The generic pharmaceutical firm cites DITROPAN XL product labeling[7] incorrectly in supporting their position that oxybutynin does not meet the nonlinear absorption of enantiomers. They believe that dose proportionality data of the parent and/or metabolite indicate that absorption of either or both enantiomers is linear. As FDA clearly states in their guidance, and as shown with additional data analysis in this supplement, nonlinear absorption of enantiomers is exhibited when the R-to-S ratio changes with the drug input rate. Drug input rate is highly dependent on the formulation.

Finally, the generic pharmaceutical firm also cites an FDA reviewer comment from the Summary Basis of Approval (SBA)[8] for DITROPAN XL, which is that "the R/S ratio of oxybutynin and desethyloxybutynin is not significantly different between Ditropan XL and oxybutynin IR." At the time of the review in 1998, the recent analysis of R-to-S concentration ratios were not available, even for the study cited in the SBA. This Supplement provides the appropriate data upon which to assess nonlinear absorption of enantiomers as suggest in FDA's 2003 guidance[9].

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[7] DITROPAN XL® [Package Insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; 2004.
[8] Ditropan XL: http://www.fda.gov/cder/foi/nda/98/20897.htm
[9] Ibid 1.

I. STATISTICAL ANALYSIS OF STUDY DATA SUPPORTS THE SCIENTIFIC AND CLINICAL BASIS OF APPLYING BIOEQUIVALENCE CRITERIA TO OXYBUTYNIN AND ITS METABOLITE

As discussed in the original Petition, clinical differences among oxybutynin products can be attributed to the relative concentrations of metabolite to parent that are influenced by various dosage form technologies, immediate- and extended-release rates, and residence times in specific regions of the gastrointestinal tract. These clinical differences include the expression and tolerability of untoward anticholinergic effects and adherence to treatment, especially in the elderly population. The overall therapeutic management of overactive bladder can be affected, because patients are commonly titrated to the most effective dose of oxybutynin, which is a balance between the improvement of symptoms and tolerability of adverse effects.

Oxybutynin and its active metabolite, desethyloxybutynin, are about equipotent in their anticholinergic effects on human bladder detrusor muscle[10] that control symptoms of overactive bladder. They both contribute to expected dose-related antimuscarinic adverse effects, such as dry mouth, nausea, constipation, and somnolence, but the metabolite is more potent than the parent in anticholinergic effects on the salivary gland[11]. These adverse effects can be severe enough to render therapy intolerable to some patients and limit their ability to continue without either lowering to a less effective dose or stopping therapy.

Plasma concentration ratios of metabolite to parent depend on the mode of administration (eg, oral, intravenous, or transdermal), pharmaceutical dosage form, and oral release rate as it relates to site-specific metabolism, the drug delivery technology, ingestion with food, and gastrointestinal transit time. Therefore, it is critically important to consider the pattern of systemic exposures to oxybutynin and desethyloxybutynin, which contribute differently to pharmacologic actions, in establishing bioequivalence between pharmaceutically equivalent or alternative extended-release oxybutynin products.

DITROPAN XL partially bypasses first-pass metabolism due to its release-rate profile and gastrointestinal transit time. The resulting lower metabolite-to-parent concentration ratio renders DITROPAN XL therapeutically distinct from other oral oxybutynin products. Data

[10] Waldeck K, Larsson B, Andersson KE. Comparison of oxybutynin and its active metabolite, N-desethyloxybutynin, in the human detrusor and parotid gland. *J Urol* 1997;157:1093-7.
[11] Ibid. 10.

from published pharmacokinetic-pharmacodynamic studies[12,13] show directly that higher metabolite concentrations are associated with less saliva production and more severe dry mouth. Patients in clinical trials[14,15] also report less untoward anticholinergic effects in general for oxybutynin products that produce less metabolite. Because overactive bladder is a chronic condition, drug therapy is most successful if it can be sufficiently tolerated by patients needing long-term treatment.

Recently a statistical analysis of the metabolite-to-parent ratios for AUCINF and CMAX was conducted with biopharmaceutical study data. Mean ratios of the pharmacokinetic parameters for the racemic mixture and for the R- and S-enantiomers were included in an analysis of variance (ANOVA) with four factors appropriate for a crossover study design: treatment, period, sequence, and subject nested within sequence. AUCINF and CMAX data for both DITROPAN XL and immediate-release tablets were available from one pharmacokinetic (C96-074) and one pharmacokinetic-pharmacodynamic (C98-041)[16] study sponsored by ALZA. Table 1 contains a summary of the results in which highly significant statistical differences were detected in mean values of metabolite-to-parent ratios for each formulation, which have different *in vivo* and *in vitro* drug release rates. The metabolite-to-parent AUCINF ratios for immediate-release tablets were about double those for DITROPAN XL for the racemic mixture and both enantiomers. The CMAX ratios for immediate-release tablets were about 25% greater.

Table 2 contains results of the statistical analysis comparing mean values of the metabolite-to-parent ratios among three DITROPAN XL treatments in ALZA Study C-96-068. This study was selected because data for two doses of extended-release oxybutynin (10 vs 20 mg) were available to assess whether the amount of drug released at the same rate may affect the metabolite-to-parent ratios. The results in Table 2 show that the 20-mg dose did not affect the metabolite-to-parent AUCINF and CMAX ratios for the racemic mixture and pharmacologically active, R-enantiomer, when compared with the either treatment cell containing the 10-mg dose. Statistically significant differences in mean ratios for both AUCINF and CMAX were detected for the less active S-enantiomer. At the higher dose,

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[12] Sathyan G, Chancellor MB, Gupta SK. Effect of OROS controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. *Br J Clin Pharmacol* 2001;52:409-417.

[13] Lukkari E, Aranko K, Juhakoski A, *et al.* Effect of time interval between food and drug ingestion on the absorption of oxybutynin from a controlled-release tablet. *Pharmacol Toxicol* 1997;81:31-4.

[14] NDA 20-897, December 1997

[15] Davila GW, Daughtery CA, Sanders SW, *et al.* a short term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J Urol* 2001;166(1):140-5.

[16] Ibid. 12.

more S-oxybutynin was metabolized to S-desethyloxybutynin, suggesting dose-dependent pharmacokinetics of this enantiomer.

The clinical relevance of relative metabolite-to-parent systemic exposure was discussed in the original Petition. Collectively, the clinical study data indicate that differences among oxybutynin products in the expression and tolerability of untoward anticholinergic effects, and adherence to treatment by patients, can be attributed to these relative differences in metabolite and parent concentrations. Pharmacokinetic data show that the metabolite-to-parent AUC_{INF} and C_{MAX} ratios are strongly dependent on drug release rate. For extended-release oxybutynin products, bioequivalence decisions based solely on oxybutynin plasma concentrations are insufficient without consideration of desethyloxybutynin and the inherent stereoselective differences of both active moieties. This can lead to the inappropriate approval of generic products deemed bioequivalent, which ultimately prove to have very different adverse effect and safety profiles once in widespread use for overactive bladder.

Table 1. Effect of Drug Input (Release) Rate on Racemic and Enantiomer Metabolite-to-Parent Ratios[a,b]

ALZA Study Number	Oxybutynin Dosage Form	Daily Dose	Test	Total-Des/Oxy AUCINF	R-Des/Oxy AUCINF	S-Des/Oxy AUCINF	Total-Des/Oxy CMAX	R-Des/Oxy CMAX	S-Des/Oxy CMAX
C-96-074-02	*Extended-Release* OROS Osmotic Tablet	A. 2 X 5 mg two in am		5.13 (1.12) 21.7%	9.13 (2.26) 24.8%	3.00 (0.53) 17.7%	5.35 (1.55) 29.0%	10.3 (3.78) 36.7%	2.91 (0.67) 23.0%
	Extended-Release OROS Osmotic Tablet	B: 1 X 10 mg one in am		5.38 (0.93) 17.2%	9.57 (1.93) 20.16	3.14 (0.53) 16.8%	6.04 (1.99) 33.0%	11.4 (4.15) 36.4%	3.27 (0.96) 29.3%
	Immediate-Release Disintegrating Tablet	D: 3 X 5 mg one every 4h		11.4 (2.35) 20 7%	19.0 (4.70) 24.7%	6.09 (1.18) 19.4%	6.50 (2.13 32.7%	12.9 (4.67) 36.3%	3.28 (0.96) 29.2%
			A vs D	p < 0.001	p < 0.001	p < 0.001	p = 0.006	p = 0.002	p = 0.050
			B vs D	p < 0.001	p < 0.001	p < 0.001	p = 0.184	p = 0.036	p = 0.946
C-98-041	*Extended-Release* OROS Osmotic Tablet	A: 1 X 10 mg one in am		4.40 (0.66) 15.1%	7.64 (1.83) 24.0%	2.52 (0.35) 14.0%	4.38 (0.84) 19.1%	7.81 (1.88) 24.1%	2.45 (0.45) 18.4%
	Immediate-Release Disintegrating Tablet	B: 2 X 5 mg one every 8h		9.65 (2.06) 21.3%	16.1 (4.30) 26.7%	5.14 (1.07) 20.8%	6.79 (2.13) 31.3%	12.6 (4.60) 36.4%	3.36 (0.97) 29.0%
			A vs B	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001

[a] Data on File, 9/05

[b] Results are reported as mean, (standard deviation), and % coefficient of variation

Key. Oxy – oxybutynin; Des – desethyloxybutynin; am – morning; CMAX – maximum exposure or plasma concentration, ng/mL; AUCINF – total systemic exposure, or area under the curve extrapolated to infinity, ng•hr/mL, for the one day of dosing in Study C-96-074-02, but is AUC0-24 on the fourth day of dosing in Study C-98-041.

Table 2. Effect of Oxybutynin Dose on Racemic and Enantiomer Metabolite-to-Parent Ratios[a,b]

ALZA Study Number	Oxybutynin Dosage Form	Daily Dose[c]	Test	Total-Des/Oxy AUC_{INF}	R-Des/Oxy AUC_{INF}	S-Des/Oxy AUC_{INF}	Total-Des/Oxy C_{MAX}	R-Des/Oxy C_{MAX}	S-Des/Oxy C_{MAX}
C-96-068	*Extended-Release* OROS Osmotic Tablet	A: 2 X 5 mg two in am		5.35 (3.14) 58.6%	8.58 (1.79) 20.9%	3.02 (0.78) 25.7%	6.20 (1.97) 31.8%	11.23 (3.67) 32.6%	3.34 (0.96) 28.7%
		B: 1 X 10 mg one in am		5.25 (2.55) 48.7%	8.59 (2.65) 30.9%	2.89 (0.54) 18.8%	6.07 (1.93) 31.8%	11.20 (3.86) 34.4%	3.27 (0.92) 28.3%
		C: 4 X 5 mg four in am		4.71 (1.42) 30.3%	8.78 (1.97) 22.4%	3.25 (0.90) 27.7%	6.45 (1.79) 27.8%	11.19 (3 15) 28.1%	3.60 (0.95) 26.5%
			A vs B	p = 0.828	p = 0.985	p = 0 211	p = 0.610	p = 0.957	p = 0.574
			C vs B	p = 0.259	p = 0.579	p = 0.001	p = 0.145	p = 0.975	p = 0.009
			C vs A	p = 0.180	p = 0.566	p = 0.023	p = 0.340	p = 0.932	p = 0.038

[a] Data on File, 9/05
[b] Results are reported as mean, (standard deviation), and % coefficient of variation
[c] Each daily dose of one or more OROS tablets was swallowed in the morning after an overnight fast.

Key: Oxy – oxybutynin; Des – desethyloxybutynin; am – morning; AUC_{INF} – total systemic exposure or area under the curve extrapolated to infinity, ng•hr/mL; C_{MAX} – maximum exposure or plasma concentration, ng/mL

II. REQUEST THAT BIOEQUIVALENCE CRITERIA BE APPLIED SEPARATELY TO OXYBUTYNIN AND DESETHYLOXYBUTYNIN ENANTIOMERS TO ENSURE THERAPEUTIC EQUIVALENCE

A. Statement of the Issue and Requested Action

For the majority of drugs, the active moiety is the administered drug substance and not any of its metabolites. There are exceptions in which the drug substance is inactive (eg, acts as a prodrug) and the major metabolite is active, or both parent and metabolite are active. For chiral drug substances, which are most often administered as the racemic mixture (50% of each stereoisomer), one enantiomer may be the active moiety or both enantiomers are active but may have different pharmacologic effects or potencies. FDA has provided guidance[17] for establishing bioequivalence of drug products with enantiomers having different activities that meaningfully contribute to safety and efficacy.

FDA recommends[18] that bioequivalence of individual enantiomers be determined when four conditions are met: (i) nonlinear absorption is present for at least one enantiomer in which the enantiomer concentration ratio changes with the input rate of the drug, (ii) enantiomers exhibit different pharmacokinetics, (iii) enantiomers exhibit different pharmacodynamics, and (iv) primary efficacy and safety activity resides with the minor enantiomer.

In this Supplement, Ortho Urology presents scientific evidence demonstrating that oxybutynin exhibits nonlinear absorption in which the enantiomer concentration ratio changes with the drug input rate. Scientific and clinical evidence, provided in the original Petition and summarized herein, shows that the oxybutynin enantiomers exhibit different pharmacokinetic and pharmacodynamic characteristics, and that the primary safety and efficacy activity resides with the minor enantiomer (R-oxybutynin). Oxybutynin is a chiral drug that meets the four conditions for which bioequivalence of individual enantiomers should be determined.

Ortho Urology, therefore, requests that FDA requires that bioequivalence criteria be applied separately to the R- and S-enantiomers of both oxybutynin and desethyloxybutynin to ensure bioequivalence and true therapeutic equivalence of extended-release oxybutynin

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[17] FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. March 2003: pp. 17-19.

[18] Ibid 1. pp 18-19.

products. Moreover, application to the four active moieties[19] of oxybutynin should be required in bioequivalence studies conducted under both fasting and fed conditions.

1. Oxybutynin Enantiomer(s) Exhibits Nonlinear Absorption Dependent on Drug Input Rates

For chiral drugs that exhibit linear absorption of both enantiomers, plasma concentrations of each enantiomer will vary only in direct proportion to dose and the relative proportions of the R- and S-enantiomers remain constant with any variations in the input rate. When the pharmacokinetics of one enantiomer is nonlinear, then the relative proportion of the two enantiomers will vary depending on the input rate. In the latter situation, the R-to-S concentration ratio is susceptible to changes in *in vivo* absorption rate and is, thus, formulation dependent.

The rate and extent of absorption is expressed by CMAX and AUCINF, respectively. Because AUCINF is viewed as a more accurate index of drug exposure than single-point plasma concentrations over a pharmacokinetic profile, the R-to-S AUCINF ratio is more sensitive to, and reflective of, nonlinear absorption of either or both enantiomers. The R-to-S CMAX ratio is not as sensitive because, if there is nonlinear absorption of either or both enantiomers, the enantiomers will reach their maximum concentrations at different times. Therefore, the R-to-S CMAX ratio is approximated as the ratio of each enantiomer plasma concentration at the time point of CMAX for the racemic mixture. In addition, accurate estimates of CMAX depend on the frequency of blood sampling, which may be optimal for one enantiomer and not the other.

Oxybutynin is a chiral drug that is metabolized into the active desethyloxybutynin metabolite primarily by cytochrome P450 3A4 (CYP3A4) isoenzyme. It undergoes extensive and variable, presystemic, first-pass metabolism, resulting in a low mean oral bioavailability of about 6%.[20] The upper small intestine serves as the major site for intestinal CYP3A-mediated first-pass metabolism, which is mainly passed by the extended-release DITROPAN XL tablets. In addition, the metabolism of oxybutynin is stereoselective for the active R-enantiomer.

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[19] 21 CFR § 320.24(b)(1)(i).

[20] Douchamps J, Derenne F, Stockis A, *et al* The pharmacokinetics of oxybutynin in man. *Eur J Clin Pharmacol* 1988;35:515-20.

Oxybutynin absorption is affected by differences in the pharmaceutical dosage form (eg, formulations and delivery technologies) and drug release rate, which are further compounded by individual differences in physiology of gastrointestinal tract and distribution of CYP3A4. Even at the same daily dose, bioavailabilities of R- and S-enantiomers of the parent and active metabolite are often markedly different because of differences in drug release rates among immediate- and extended-release oxybutynin products coupled with site-specific gut-wall metabolism.

Drug input rate will vary among oxybutynin products depending on delivery technologies and release rates. The DITROPAN XL OROS tablet is comprised of an osmotically active bilayer core surrounded by a semipermeable membrane. In the gastrointestinal tract, water permeates the membrane and causes drug to suspend and the push layer to expand, forcing oxybutynin out a laser-drilled orifice. The semipermeable membrane controls water permeation into the tablet core, which in turn controls the rate of drug delivery. Unlike OROS, immediate-release tablets disintegrate quickly upon ingestion, exposing oxybutynin to the upper small intestine and greater CYP3A4 metabolism to desethyloxybutynin. Another extended-release oxybutynin product available only in Finland, CYSTRIN CR®, is comprised of a hydrophilic matrix[21] that slowly expands and erodes in an aqueous environment to release oxybutynin. CYSTRIN CR also has a unique pattern of parent to metabolite plasma concentrations.

For DITROPAN XL, bioavailability differences of the R- and S-enantiomers of parent and metabolite relative to those for an immediate–release tablet illustrate the differences in drug input rate and the stereoselective metabolism of oxybutynin.[22] The relative bioavailability for R-oxybutynin is lower at 156% compared with 187% for the S-enantiomer, but both parent enantiomers are more bioavailable (>100%) when dosed using OROS extended-release tablets. The latter findings are consistent with bypassing some upper small intestinal metabolism to desethyloxybutynin. The relative bioavailabilities for R- and S-desethyloxybutynin were lower for DITROPAN XL at 73% and 92%. Changes in the relative bioavailabilities of each active moiety, primarily due to release rate differences between the immediate- and extended-release formulations and site-specific metabolism, lead to a different pattern of exposure for the parent drug and metabolite, and therefore, a different safety and efficacy profile[23]. Moreover, the bioavailability of the S-enantiomer for

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[21] http://media.corporate-ir.net/media_files/irol/90/90346/reports/penwest2004ar.pdf accessed 8/22/05.
[22] NDA 20-897, ALZA Clinical Study Report C-96-074-02, 12/1997.
[23] Gupta SK, Sathyan G, Lindemulder EA, *et al.* Quantitative characterization of therapeutic index: Application of mixed-effects modeling to evaluate oxybutynin dose-efficacy and dose-side effect relationships. *Clin Pharmacol Ther* 1999;65:672-84.

both oxybutynin and desethyloxybutynin was statistically significantly higher than that of the R-enantiomer ($p<0.05$, paired t-test), indicating that the R-to-S ratio differs between immediate-release and OROS tablets. If the ratios were the same, then the bioavailabilities of both enantiomers would also be the same.

Because of the differences in oxybutynin input rates between immediate-release and OROS tablets and in stereoselective metabolism, Ortho Urology conducted a *post-hoc* analysis of pharmacokinetic data from ALZA Studies C-96-074-02, C-98-041, and C-96-068 to determine if oxybutynin enantiomers exhibit nonlinear absorption. The effects of drug input rate and dose (at the same input rate) on absorption, expressed as the R-to-S ratios of AUC_{INF}, were determined. As stated previously, the R-to-S AUC_{INF} ratio is more sensitive to, and reflective of, nonlinear absorption of either or both enantiomers. For completeness, however, the R-to-S C_{MAX} ratios were approximated as the ratio of R- and S-enantiomer plasma concentrations reported at the time point of the racemic C_{MAX}.

The effect of drug input rate on nonlinear absorption of the enantiomers is illustrated with the R-to-S AUC_{INF} and AUC_{0-24} ratios for oxybutynin and desethyloxybutynin in Studies C-96-074-02 and C-98-041, respectively. Differences in mean ratios of R-to-S AUC_{INF}, AUC_{0-24}, and C_{MAX} were tested by ANOVA with four factors appropriate for a crossover study design: treatment, period, sequence, and subject nested within sequence. Results of the statistical analysis are summarized in Table 3. In Study C-96-074-02, the R-to-S AUC_{INF} ratios for both oxybutynin and desethyloxybutynin were greater ($p<0.001$) for the immediate-release tablet, administered at the daily dose of 15 mg oxybutynin (one 5-mg tablet every four hours), compared with the OROS tablet, administered as 10 mg oxybutynin (two 5-mg OROS tablet at once). As expected, results for the less sensitive R-to-S C_{MAX} ratios were mixed, with one comparison statistically significant, one borderline, and two not significant.

In Study C-98-041, 10 mg oxybutynin was administered daily for four days as either one 5-mg immediate-release tablet every eight hours or one 10-mg OROS tablet. In this study, AUC_{0-24} is the area under the curve over the daily dosing interval, and was estimated after the final doses on the fourth day. Comparing the immediate- and extended-release tablets, statistically significant differences ($p<0.001$) in mean values of the R-to-S AUC_{0-24} ratios for oxybutynin and desethyloxybutynin were detected. Differences in means for R-to-S C_{MAX} ratios were also significant at $p = 0.021$ and 0.035 for parent and metabolite, respectively. These results confirm the findings in Study C-96-074-02, and together they demonstrate that at least one enantiomer of oxybutynin exhibits nonlinear absorption such that the enantiomer concentration ratio changes with drug input rate. Mean R-to-S AUC_{INF} and

AUC_{0-24} ratios for the immediate-release tablet were about 25 to 30% higher than those for DITROPAN XL. This finding of enantiomer nonlinear absorption has important implications for establishing bioequivalence between extended-release oxybutynin products that have different *in vitro* and *in vivo* release rates, and transit times in the gastrointestinal tract due to delivery technology. Bioequivalence criteria should be applied to the four moieties: the R- and S-enantiomers of oxybutynin and desethyloxybutynin.

The effect of dose on nonlinear absorption of the enantiomers was assessed with the R-to-S AUC_{INF} ratios for oxybutynin and desethyloxybutynin in Study C-96-068. The R-to-S C_{MAX} ratios were also approximated. Oxybutynin was administered at 10- and 20-mg doses as OROS tablets, thus having the same release rate: (A) 10 mg as two 5-mg tablets, (B) 10 mg as one 10-mg tablet, and (C) 20 mg as four 5-mg tablets. Table 4 contains results of the statistical analysis in which the mean R-to-S AUC_{INF} ratios did not show a difference for either oxybutynin or desethyloxybutynin. These results indicate that the dose of oxybutynin did not affect absorption of the enantiomers when administered as tablets having the same *in vitro* and *in vivo* release rates. Although no statistical differences were detected in mean R-to-S C_{MAX} ratios for desethyloxybutynin, they were detected in mean R-to-S C_{MAX} ratios for oxybutynin for the 10- versus 20-mg dose comparisons.

Collectively, these data analyses show that the input rate of oxybutynin, and not the dose, affects the R-to-S AUC_{INF} ratios for oxybutynin and desethyloxybutynin, demonstrating that the absorption of oxybutynin is nonlinear with regard to its enantiomers. Therefore, oxybutynin meets the first condition in which nonlinear absorption is present for at least one enantiomer such that the enantiomer concentration ratio changes with the input rate of the drug. Although this scientific characteristic of oxybutynin was illustrated by comparing available data for an immediate-release tablet and extended-release OROS tablet, nonlinear absorption that depends on release rate should be considered in other extended-release products that have different *in vitro* and *in vivo* release rates and/or drug delivery technologies (eg, osmotic tablet, matrix tablet, and coated beads).

Table 3. Effect of Drug Release or Input Rate on R-to-S Enantiomer Ratios of Oxybutynin and Desethyloxybutynin[a,b]

				R-to-S AUC_{INF} Ratio		R-to-S C_{MAX} Ratio	
ALZA Study Number	**Oxybutynin Dosage Form**	**Daily Dose**	**Test**	**R-Oxy / S-Oxy**	**R-Des / S-Des**	**R-Oxy / S-Oxy**	**R-Des / S-Des**
C-96-074	*Extended-Release* OROS Osmotic Tablet	A: 2 X 5 mg two in am		0.55 (0.12)	1.66 (0.46)	0.52 (0.10)	1.798 (0.43)
	Extended-Release OROS Osmotic Tablet	B: 1 X 10 mg one in am		0.55 (0.11)	1.70 (0.46)	0.53 (0.10)	1.84 (0.48)
	Immediate-Release Disintegrating Tablet	D: 3 X 5 mg one every 4h		0.69 (0.16)	2.16 (0.63)	0.48 (0.18)	1.92 (0.29)
			A vs D	$p < 0.001$	$p < 0.001$	$p = 0.113$	$p = 0.021$
			B vs D	$p < 0.001$	$p < 0.001$	$p = 0.060$	$p = 0.105$
C-98-041	*Extended-Release* OROS Osmotic Tablet	A: 1 X 10 mg one in am		0.59 (0.10)[c]	1.82 (0.54)[c]	0.58 (0.10)	1.87 (0.51)
	Immediate-Release Disintegrating Tablet	B: 2 X 5 mg one every 8h		0.72 (0.14)[c]	2.28 (0.65)[c]	0.51 (0.14)	2.03 (0.37)
			A vs B	$p < 0.001$	$p < 0.001$	$p = 0.021$	$p = 0.035$

[a] Results are reported as mean (standard deviation)
[b] Data on File, 9/05
[c] AUC from study C-98-041 is AUC over the daily dosing interval of 24 hours (AUC_{0-24}) on the fourth day

Key: Oxy – oxybutynin; Des – desethyloxybutynin; am – morning; AUC_{INF} – total systemic exposure or area under the curve extrapolated to infinity, ng•hr/mL; C_{MAX} – maximum exposure or concentration, ng/mL

Table 4. Effect of Dose on R-to-S Enantiomer Ratios of Oxybutynin and Desethyloxybutynin[a,b]

				R-to-S AUCINF Ratio		R-to-S CMAX Ratio	
ALZA Study Number	Oxybutynin Dosage Form	Daily Dose	Test	R-Oxy / S-Oxy	R-Des / S-Des	R-Oxy / S-Oxy	R-Des / S-Des
C-96-068	*Extended-Release* OROS Osmotic Tablet	A. 2 x 5 mg two in am		0.58 (0.12)	1.69 (0.50)	0.56 (0.12)	1.92 (0.42)
	Extended-Release OROS Osmotic Tablet	B: 1 x 10 mg one in am		0.56 (0.09)	1.68 (0.56)	0.55 (0.11)	1.93 (0.42)
	Immediate-Release Disintegrating Tablet	C: 4 x 5 mg four in am		0.58 (0.14)	1.65 (0.57)	0.60 (0.11)	1.92 (0.46)
			A vs B	p = 0.234	p = 0.820	p = 0.789	p = 0.920
			C vs A	p = 0.684	p = 0.308	p = 0.031	p = 0.870
			C vs B	p = 0.112	p = 0.427	p = 0.016	p = 0.791

[a] Results are reported as mean (standard deviation)
[b] Data on File, 9/05

Key: Oxy – oxybutynin; Des – desethyloxybutynin; am – morning; AUCINF – total systemic exposure or area under the curve extrapolated to infinity, ng•hr/mL; CMAX – maximum exposure or concentration, ng/mL

2. *Pharmacologic Activity and Human Pharmacodynamics Differs Among Oxybutynin, Desethyloxybutynin, and Their Enantiomers*

Muscarinic receptors are widely distributed throughout body, and have been classified into five subtypes (M_1 to M_5). The human detrusor muscle of the bladder contains a mixed population of M_2 and M_3 subtypes. Although the M_2 predominates at about 80%, bladder contraction is mediated by M_3 receptors.[24] Oxybutynin's anticholinergic activity, relative binding to antimuscarinic receptor subtypes (M_1, M_2, and M_3), and cystometric activity are stereoselective in animal tissues.[25,26] The R-oxybutynin enantiomer has been shown to exert higher anticholinergic activities than the racemic mixture and S-enantiomer[27], the latter of which contribute more to the spasmolytic effects of oxybutynin.[28]

Pharmacologic studies using human tissue from the detrusor muscle and salivary gland show that oxybutynin's metabolite, desethyloxybutynin, also acts as a competitive antagonist at muscarinic receptors.[29] Although oxybutynin and desethylbutynin have similar binding characteristics and *in vitro* antimuscarinic effects, the affinity of the metabolite to receptors in the salivary gland is significantly higher than that of the parent.[30] Because desethyloxybutynin exhibits antimuscarinic activity, the rate and extent of its formation will influence the time course and amplitude of both clinical and untoward anticholinergic effects, such as lowering saliva production, which leads to dry mouth.

3. *Stereoselective Metabolism and Pharmacokinetics of Oxybutynin*

Oxybutynin exhibits stereoselective metabolism and pharmacokinetics in which preferential oxidation of R-oxybutynin leads to its lower bioavailability compared with the S-enantiomer,

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[24] Wang P, Luthin Gr, Ruggieri MR. Muscarinic acetylcholine receptor subtypes mediating urinary bladder contractility and coupling to GTP binding proteins. *J Pharmacol Exp Ther* 1995;273:959-66.

[25] Kachur JF, Peterson JS, Carter JP. R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine. *J Pharmacol Exp Ther* 1988;247:867-72.

[26] Noronha-Blob L, Kachur JF. Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2, and M3 muscarinic receptors and *in vivo* effects on urinary bladder contraction, mydriasis, and salivary secretion in guinea pigs. *J Pharmacol Exp Ther* 1991;256:562-7.

[27] Ibid. 26.

[28] Smith ER, Wright SE, Aberg G. Comparison of Antimuscarinic and antispasmolytic actions of racemic oxybutynin and desethyloxybutynin and their entantiomers. *Arzneim Forsch Drug Res.* 1998;48:1012-8.

[29] Ibid. 10.

[30] Ibid. 10.

and significantly higher systemic exposure to R-desethyloxybutynin. In a pharmacokinetics study[31] that evaluated a 5-mg immediate-release tablet, mean metabolite-to-parent ratios of the R-enantiomers for CMAX and AUCINF were about 8.9 and 21.5, respectively, whereas they were only 3.3 and 8.3, respectively, for the S-enantiomers. In the same study, a transdermal patch had metabolite-to-parent ratios of the R- and S-enantiomers for CMAX and AUCINF that ranged from only 0.8 to 1.0. These marked differences in the concentration ratios between the modes of administration (oral having very high ratios and transdermal having ratios near unity), and between the enantiomer ratios after oral administration, are highly consistent with oxybutynin's extensive presystemic gut-wall oxidation by CYP3A4 isoenzymes and with the stereoselective metabolism of the R-enantiomer.

For DITROPAN XL, bioavailabilities of the R- and S-enantiomers of parent and metabolite relative to those for an immediate–release tablet further illustrates the stereoselective metabolism of oxybutynin.[32] The relative bioavailability for R-oxybutynin is lower at 156% compared with 187% for the S-enantiomer, but both parent enantiomers are more bioavailable (>100%) when dosed using OROS extended-release tablets. The latter findings are consistent with bypassing some upper small intestinal metabolism to desethyloxybutynin. The relative bioavailabilities for R- and S-desethyloxybutynin were lower for DITROPAN XL at 73% and 92%.

The distribution of isomers does not appear to be affected by post absorption mechanisms as the inversion of the S-enantiomer of both oxybutynin and desethyloxybutynin does not occur *in vivo.* In a pharmacokinetics study[33] in which only S-oxybutynin (5 to 320 mg) was dosed in healthy men and women, neither R-oxybutynin nor R-desethyloxybutynin were detected in plasma. No pharmacokinetics studies dosing only R-oxybutynin have been conducted, so it is unknown whether the R configuration of either the parent or metabolite inverts to the S configuration.

4. Primary Efficacy and Safety Activity Resides With the Minor Enantiomer

R-oxybutynin is the minor enantiomer as defined by total systemic exposure relative to that of the S-enantiomer. Stereoselective metabolism of racemic oxybutynin decreases the

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[31] Zobrist RH, Schmid B, Feick A, et al. Pharmacokinetics of the R- and S-enantiomers of oxybutynin and N-desethyloxybutynin following oral and transdermal administration of the racemate in healthy volunteers. *Pharmaceut Res* 2001;18:1029-34.

[32] ALZA Clinical Study Report C-96-074-02 submitted in NDA 20-897.

[33] Koch P, McCullough, Blum PS, et al. Pharmacokinetics and safety of (s)-oxybutynin in normal healthy volunteers. [abstract # 825] *FASEB* 1998;12:A142.

bioavailability of R-oxybutynin such that its concentrations (CMAX and AUCINF) are less than those for S-oxybutynin for oral pharmaceutical dosage forms. However, R-oxybutynin compared with S-oxybutynin is primarily responsible for the anticholinergic effects of oxybutynin that determine both clinical efficacy and safety in the treatment of overactive bladder.

In one study assessing *in vivo* activity,[34] R-oxybutynin was 21- to >100-fold more potent than S-oxybutynin at inhibiting bladder volume-induced contractions, 136-fold more potent at inducing mydriasis, and 30-fold more potent at inhibiting salivation. R-oxybutynin also was reported to be more potent than S-oxybutynin in another study utilizing several *in vitro* and *in vivo* assays related to the safety and efficacy of oxybutynin.[35] Thus, although plasma concentrations of R-oxybutynin are lower than S-oxybutynin after administration of racemic drug formulations,[36] this minor enantiomer contributes greater pharmacologic activity. Differences among oral oxybutynin agents with respect to plasma concentrations of the R-enantiomer due to dissimilar transit times and site-specific metabolism could result in differences in the balance between drug tolerability and efficacy, and result in divergent clinical outcomes.

The concentration-effect relationship between each R-enantiomer and dry mouth was evaluated in a double-blind, pharmacokinetics-pharmacodynamics study[37] comparing four days of dosing with DITROPAN XL 10mg in the morning and immediate-release oxybutynin 5 mg in the morning and eight hours later. The decrease in salivary output and consequent increase in dry mouth severity on a 100 mm visual analogue scale were correlated with plasma R-desethyloxybutynin concentrations, but no relationship with R-oxybutynin concentrations was observed. These results further support that the both safety and efficacy of oxybutynin resides primarily with the R-enantiomers.

III. CONCLUSIONS

For extended-release oral oxybutynin products, bioequivalence decisions based solely on racemic oxybutynin plasma concentrations are insufficient without consideration of desethyloxybutynin and the inherent stereoselective differences of both active moieties. This can lead to the inappropriate approval of generic products deemed bioequivalent,

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[34] Ibid. 26.
[35] Ibid. 25.
[36] Sathyan G, Hu W, Gupta SK. Lack of effect of food on the pharmacokinetics of an extended-release oxybutynin formulation. *J Clin Pharmacol* 2001;41:187-92.
[37] Ibid. 12.

which may ultimately prove to have very different adverse effect and safety profiles once in widespread use for overactive bladder.

- Scientific and clinical study data demonstrate that oxybutynin meets the four conditions in FDA's guidance such that bioequivalence of individual R- and S-enantiomers should be determined. Differences among oxybutynin products in the expression and tolerability of untoward anticholinergic effects and adherence to treatment by patients can be attributed to differences in R and S concentrations. Stereoselective metabolism and pharmacologic activities further support the application of bioequivalence criteria to the four active moieties of oxybutynin.
- ALZA Corporation developed DITROPAN XL and recognized the importance of delineating the pattern of systemic exposures. They assessed the four moieties in all pivotal pharmacokinetics, bioavailability, and bioequivalence studies submitted in NDA 20-897, and pertinent information is provided in the product label. Consistent with this standard, bioequivalence of the clinical and commercial OROS formulations was established by applying FDA's bioequivalence metrics and confidence interval criteria *a priori* to the R- and S-enantiomers of oxybutynin and desethyloxbutynin.[38]

Therefore, Ortho Urology requests that FDA require, rather than recommend, that bioequivalence criteria be applied to the R– and S- enantiomers of oxybutynin and desethyloxybutynin in fasted and fed studies to ensure clinical equivalence of extended-release oxybutynin products.

[38] ALZA Clinical Study Report C-97-015-01 submitted in NDA 20-897.

C. ENVIRONMENTAL IMPACT

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. §§ 25.22 and 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), Ortho Urology will provide data concerning the economic impact of the relief requested should such information be requested by FDA.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petitioner.

Very truly yours,
Ortho-McNeil Pharmaceutical, Inc.

Minnie Baylor-Henry
Vice-President, Medical and Regulatory Affairs